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(54) Title: NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS

(57) Abstract: The present invention is directed to a solid formulation comprising the mixture of a lipid regulating agent and an excipient, in which said agent and said excipient form a eutectic mixture.

Novel Formulations Comprising Lipid-Regulating Agents

Field of the Invention

The present invention relates to novel formulations comprising lipid-regulating agents.

Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said intermediate layer is formed.

European Patent Application No. EP 744,958A discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granules thus produced are dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

Sheu, M. T., et al, *Int. J. Pharma.* 103 (1994) 137-146, reported that it is possible that the enhancement of dissolution rate by PEG 6000 might arise from the reduction of particle size and/or increase in wettability.

Palmieri, G. F., *Pharma Sciences* 6 (1996) 188-194, reported that drug solid solutions are formed when the amount of fenofibrate in the powder is below 15%, and that drug solubility is increased by the formation of solid

dispersion, particularly for the ratio of 90:10 carrier:drug.

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely divided particles of pure gemfibrozil granulated with a pharmaceutically-acceptable water soluble or insoluble polymer which are then uniformly coated with a pharmaceutically-acceptable (meth)acrylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as

prevastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

It is an object of the present invention to provide formulations of lipid-regulating agents having enhanced bioavailability when compared to commercially available formulations.

Summary of the Invention

The present invention is directed to a solid formulation comprising the mixture of a lipid-regulating agent and an excipient, such as polyethylene glycol, in which said agent and said excipient form a eutectic mixture. The size reduction obtained through the preparation of a dispersion is usually difficult to obtain. However, by using a fusion technique or solvent evaporation technique, a dispersion of crystalline lipid-regulating agent is prepared in the excipient such that said agent and said excipient form a eutectic mixture. The resulting formulation results in an increase in drug solubility and oral bioavailability, and an improved dissolution rate.

The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into hard gelatin shells or capsules or compressed into tablets for administration, or administered by other means obvious to those skilled in the art.

Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fed dogs of the formulation of Example 1 and a reference compound.

Detailed Description of the Invention

The bulk lipid-regulating agent may be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S. Patent No. 4,058,552, or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

The composition comprising the lipid-regulating agent and the excipient in a ratio such that the melting point of both the lipid regulating agent and the excipient is reduced to a single value lower than the melting point of either component is first determined. This composition, i.e. the composition at which the two components exhibit a single melting point, is called the eutectic mixture. A composition of the lipid-regulating agent and the excipient, ranging from about 0.5% (w/w) to about 10% higher than the eutectic mixture, is then heated to a sufficient temperature to obtain a clear solution. The solution is then cooled until a solid mass is formed. As an alternate method, these components at the above mentioned composition range may be dissolved in a suitable solvent to obtain a clear solution. In this latter case, it is necessary to remove the solvent to obtain the solid mass. The solid mass may then be ground, sized and optionally formulated into an appropriate delivery system.

The delivery system of the present invention results in increased dissolution rate and bioavailability, and improved dissolution rate of the lipid-regulating agent.

The term "eutectic mixture" refers to a two phase crystalline system that has a melting point that is lower than that of either pure component of the mixture. The presence of a eutectic mixture can be determined by thermal analysis and powder x ray diffractometry.

Suitable excipients include, for example, polyethylene glycol (PEG), pentaerythritol, pentaerythritol tetraacetate, succinic acid, urea, polyoxyethylene stearates, and poly-ε-caprolactone, or more preferably, PEG.

If a solvent evaporation technique is used, the suitable solvents include, for example, methanol-water, ethanol-water, or other water-miscible organic solvent in which the lipid regulating agent and the polymers have appreciable solubility.

Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include, for example, lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, or disintegrants that might be needed to prepare a capsule or tablet.

The resulting composition comprising the lipid-regulating agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The said composition can be used to improve the oral bioavailability and solubility of said lipid-regulating agent.

The invention will be understood more clearly from the following non-limiting representative examples:

Example 1

Fenofibrate and PEG in a ratio of 15:85 was heated to about 85°C until a clear solution was obtained. The solution was then cooled over an ice bath resulting in the formation of a solid mass. The resulting dry solid mass was then ground and sized through a 60-100 mesh screen. 446.7 mg. of the granular formulation (containing 67 mg. fenofibrate) was filled into individual capsules.

Example 2

Mixtures of a statin and PEG are prepared and the melting points of these mixtures are determined to locate the eutectic composition. Then the statin and PEG in a ratio that is preferably less than the eutectic composition or to about 10% higher than the eutectic composition is melted to obtain a clear solution, then the solution is cooled over ice bath to form a solid mass. This solid mass is ground and sifted between 60-100 mesh and filled into capsules to contain the appropriate desired dose.

Example 3

Capsules prepared by the process described in Example 1, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fournier) (Reference), were administered to a group of dogs at a dose of 67 mg fenofibrate/dog. The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figure 1 presents the resulting data in graph form. The results provided as mean ± SD, n=3, were as follows:

Lipanthyl 67M (Reference):
Cmax = 2.83 ± 1.40 mcg/ml
Tmax = 1.7 ± 0.6 hr
$t_{1/2}$ = 14.5 hr
AUC (0-24) = 16.36 ± 6.93 mcg•hr/ml

Capsule of Example 1:
Cmax = 5.20± 1.15 mcg/ml
Tmax = 1.3 ± 0.6 hr
$t_{1/2}$ = 10.8 hr
AUC relative to Reference = 149.08%

Claims

1. A composition comprising the mixture of a lipid-regulating agent and an excipient, in which said agent and said excipient form a eutectic mixture.

2. A composition of claim 1 wherein the lipid-regulating agent is present in the composition in an amount ranging from about 0.5% w/w to about 10% by weight above the eutectic mixture.

3. A composition of claim 1 wherein said lipid-regulating agent is a fibrate.

4. A composition of claim 3 wherein said fibrate is fenofibrate.

5. A composition of claim 1 wherein said lipid-regulating agent is a statin.

6. A composition of claim 5 wherein said statin is prevastatin.

7. A composition of claim 5 wherein said statin is atorvastatin.

8. A composition of claim 1 wherein said excipient is selected from polyethylene glycol, pentaeythritol, pentaeythritol tetraacetate, succinic acid, urea, polyoxyethylene stearates, and poly-ε-caprolactone.

9. A composition of claim 8 wherein said excipient is polyethylene glycol.

10. A delivery system comprising a composition of claim 1.

11. A delivery system of claim 10 wherein said delivery system is a capsule or tablet.

12. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

13. A method of treating hyperlipidemia comprising the administration of a composition of claim 4 to a patient.

15. A method of treating hyperlipidemia comprising the administration of a composition of claim 11 to a patient.

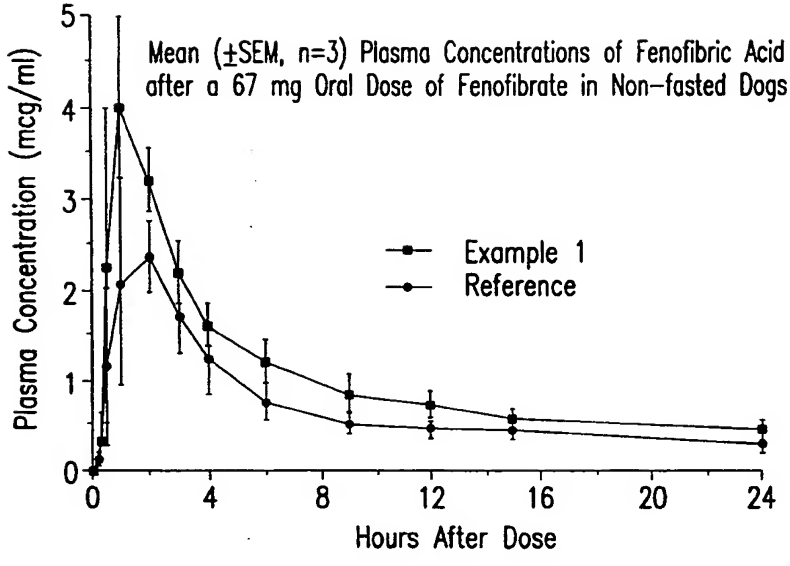
Mean (±SEM, n=3) Plasma Concentrations of Fenofibric Acid after a 67 mg Oral Dose of Fenofibrate in Non-fasted Dogs
Plasma Concentration (mcg/ml)
Hours After Dose
Example 1
Reference
0
1
2
3
4
5
0
4
8
12
16
20
24

FIG.1

INTERNATIONAL SEARCH REPORT

Int tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48 A61K47/18 A61K47/12 A61K47/26 A61K47/32
A61K47/34 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	SHEU ET AL: "Characterization and dissolution of fenofibrate solid dispersion systems" INTERNATIONAL JOURNAL OF PHARMACEUTICS,NL,AMSTERDAM, vol. 103, no. 2, 1994, pages 137-146, XP002091325 ISSN: 0378-5173 page 138, column 1, last paragraph page 138, column 2, paragraph 1 -page 139, paragraph 3; table 1 ---	1-4,8,9
X	US 4 957 746 A (VALDUCCI ROBERTO) 18 September 1990 (1990-09-18) column 1, line 45 - line 49 column 2, line 3 - line 13; claims 1-15 ---	1-3, 8-13,15
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2000	27/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Marttin, E

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/US 00/14109

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 57 201 A (BOEHRINGER MANNHEIM GMBH) 30 May 1973 (1973-05-30) page 1, line 2 - line 6 page 9, paragraph 2; example 6 claims 1,4-6	1,3, 8-13,15
A	WO 93 11749 A (WARNER LAMBERT CO) 24 June 1993 (1993-06-24) page 1, line 5 - line 24 page 4, line 25 -page 5, line 13 page 5, line 25 page 6, line 5 - line 30; claims 1-3	1,2, 10-13,15
A	MARGARIT MARIA VICTORIA ET AL: "Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000." INTERNATIONAL JOURNAL OF PHARMACEUTICS (AMSTERDAM), vol. 108, no. 2, 1994, pages 101-107, XP000929782 ISSN: 0378-5173 abstract page 102, column 1, paragraph 3 page 106, column 1, paragraph 5 - paragraph 6 page 106, column 2, line 23 - line 25	1-13,15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-13, 15 relate to a compound defined by reference to a desirable characteristic or property, namely a "lipid-regulating agent". The term "lipid-regulating agent" as used in the present independent claims 1, 10, 12, 13 and 15 and in dependent claims 2-9, and 11 defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like "lipid-regulating agent", because it is impossible to know which substances are encompassed in this expression. Moreover, a compound cannot be sufficiently characterised by the term "regulating", because this term has no well-recognised meaning and is therefore unclear. Present claims 1-13, 15 relate to a compound, defined by the term "excipient, in which said agent and said excipient form a eutectic mixture". A compound cannot be sufficiently characterised by the term "excipient, in which said agent and said excipient form a eutectic mixture", because this term is vague and unclear.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the concept of "lipid-regulating agent" and those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 3-7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. tional Application No
PCT/US 00/14109

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